Pharmacological considerations and step-by-step proposal for the treatment of Helicobacter pylori infection in the year 2018

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ABSTRACT

Over the past 30 years, multidrug regimens consisting of a proton pump inhibitor (PPI) and two or three antibiotics have been used in treating *Helicobacter pylori* (*H. pylori)* infection. In clinical practice, the optimal regimen to cure *H. pylori* infection should be decided regionally. Considering the first treatment, the Maastricht V/Florence Consensus Report and the American College of Gastroenterology Clinical Management Guideline highlight that in countries with low clarithromycin resistance rates (<15%), an empiric clarithromycin-based regimen can be used. In countries with high clarithromycin resistance rates or, in the American Guideline, with a previous exposure to clarithromycin, a bismuth-containing quadruple therapy (with metronidazole and tetracycline) is the first choice. In case of persistent infection, after a previous clarithromycin-containing regimen, this drug should be avoided in second line therapy. Options after initial eradication failure include tailored therapy (choosing antibiotic combinations based on antibiotic susceptibility testing), empiric bismuth-containing quadruple therapy or triple levofloxacin-based therapy. Encouraging data are reported, both for the first-line and for rescue treatments, with the use of a formulation of bismuth subcitrate potassium, metronidazole, and tetracycline contained in a single capsule, together with a PPI. Rifabutin- and furazolidone-based regimens should also be considered in rescue regimens. Vonoprazan, a new type of potassium-competitive acid blocker that produces more potent acid inhibition than PPIs, provides improved *H. pylori* eradication rates in combination with antibiotics. In this review, the authors provide an overview on the current knowledge on the treatment of *H. pylori* infection, with focus on therapeutic challenges in this field.

KEY WORDS: *Helicobacter pylori*- Peptic ulcer – Gastric cancer- Lymphoma-Reinfection – Resistance – Therapy –Vaccine

Introduction

After 30 years of *Helicobacter pylori* (*H. pylori*) treatment it is now evident that eradication rates with standard triple clarithromycin-based therapy, the regimen has been the most commonly used worldwide, have fallen to unacceptable levels. Choosing its replacement is challenging, as one must consider local profiles of antibiotic resistance, as well as the vast and sometimes conflicting published literature on the efficacy of various regimens that have been reported in different populations worldwide.

Pharmacological considerations in the eradication of *H. pylori*

Rationale for using proton pump inhibitors (PPIs) plus antimicrobials

PPIs are membrane permeable weak bases that accumulate in acid spaces of the active parietal cell. The PPIs are prodrugs, which are activated by acid. They then covalently bind to their target, the H^+/K^+-ATPase (proton pump), which is the ultimate mediator of acid secretion. PPIs produce far greater acid suppression than is possible with H_2 receptor antagonists.[1] There is a remarkable decrease (up to ten fold) in the activity of the main antibiotics used against *H. pylori* when the pH is reduced from 8 to 5. This is due to the fact that gastric mucosal concentration of these drugs, a key factor for *H. pylori* eradication, decreases in parallel to the reduction of pH.[2] Hence, PPIs synergize with antibiotics to eradicate *H. pylori* infection.

PPIs: optimal dosage and preferred compounds

International guidelines recommend using PPIs at a standard dose, i.e. omeprazole 20 mg, esomeprazole 40 mg, pantoprazole 40 mg, lansoprazole 30 mg or rabeprazole 20 mg, twice daily to increase the efficacy of antimicrobial regimens.[3] This is supported by systematic reviews and meta-analyses reporting significantly higher *H. pylori* eradication rates when a standard dose of PPI was

given twice compared to once daily,[4] due to higher intragastric pH values reducing both the bacterial load of *H. pylori* and the minimal inhibition concentration of antibiotics in the gastric mucosa. Another consideration regarding PPIs relates to host CYP2C19 polymorphisms, which can influence PPI metabolism. These polymorphisms have been shown to affect the efficacy of eradication therapy because 'rapid metabolizers' cannot achieve sufficiently high plasma concentration of PPIs to maintain high gastric pH during therapy.[5] However, high doses of PPIs can help overcome this effect and increase *H. pylori* eradication rates in subjects who are extensive metabolizers.[6,7] Furthermore, it has been reported that *H. pylori* eradication rates of various PPIs vary significantly according to CYP2C19 polymorphism, with differences among the PPIs in this regard. Whereas the success rates of omeprazole- and lansoprazole-containing triple therapies are affected most by CYP2C19 polymorphisms, there is no significant effect of CYP2C19 polymorphisms on rabeprazole and esomeprazole-containing regimens.[8] Based upon these considerations, the Maastricht V/Florence Consensus Report of the European Helicobacter Study Group, suggested that esomeprazole and rabeprazole may be the preferred PPIs in *H. pylori* eradication regimens in Europe and North-America, where more than half of the subjects in these regions have an extensive PPI metabolism genotype.[3]

Novel pharmacological approach to acid inhibition

Vonoprazan, a potassium-competitive acid blocker, is a new type of highly effective acid suppressant. This drug is available in Japan where it has also been approved for first- and second-line *H. pylori* eradication therapy.[9] After binding to its target (the E2-P conformation of the proton pump), vonoprazan prevents K^+ from binding, thereby inhibiting acid secretion in a K^+-competitive and reversible manner.[10] This drug is a basic compound with pKa 9.06–9.3, which is significantly higher than the pKas of conventional PPIs (lansoprazole, pKa 3.8),[11] thus enabling vonoprazan accumulation at high concentration within the low pH-secretory canaliculi of parietal cells. In addition, this drug

dissociates slowly from the proton pump, does not require acid activation, is rapidly absorbed in the intestine, and leads to fast inhibition of acid secretion.[11] Plasma half-life of 5.7 and 7 hours was reported for vonoprazan after a single 20 mg dose and on the seventh day of administration in humans, which are considerably longer than the plasma half-life of conventional PPIs (<2 h).[12] Importantly, as vonoprazan is mainly metabolized by CYP3A4, its acid inhibitory effect is least influenced by CYP2C19 polymorphisms. These features allow to this drug to exert rapid, strong, and stable inhibition of the proton pump. Vonoprazan increases intragastric pH to over 4.0 within 4 hours after the first administration in humans, creating conditions in which amoxicillin and clarithromycin are stable.[12] Consequently, the intragastric pH greater than 5 holding time ratio was reported to be 99% with vonoprazan 20 mg twice daily compared to 84% with esomeprazole at 20 mg twice daily when administered for 7 days.[13] Taken together, these observations demonstrate the improved potential of vonoprazan for eradicating *H. pylori* compared with that of conventional PPIs.

Antimicrobials: mechanisms of action and of resistance

Antimicrobial stewardship enables the optimal selection, dosage and duration of antimicrobial agents, in order to obtaining the best outcome with minimal toxicity for the patient, while minimizing the impact on bacterial resistance in the community.[14] Recently, the World Health Organization (WHO) included *H. pylori* among the 16 antibiotic-resistant bacteria that pose the greatest threat to human health. To highlight the concerns caused by increasing resistance of *H. pylori* to antibiotics, the WHO included this micro-organism, with its high proclivity to develop clarithromycin resistance, in the priority list for research and development of new antibiotics.[15] This announcement is part of a WHO campaign to improve antibiotic stewardship and reduce antibiotic misuse. In this context, it is clear that the choice of appropriate treatment for *H. pylori* infection should be based on knowledge of both local antibiotic resistance and upon outcome data. Thus, therapies recommended for one region or population may not

necessarily be identical to those used elsewhere.[3] The most widely used regimen worldwide has been standard triple therapy, consisting of a PPI, amoxicillin and clarithromycin, all taken twice daily. Nevertheless, several alternative antimicrobials are available and various combinations of them have been investigated in order to overcome increasing *H. pylori* resistance, in particular, to clarithromycin.

Based on a multicentre study published in 2013, the resistance rate of *H. pylori* in Europe was 34.9% for metronidazole, 17.5% for clarithromycin, 14.1% for levofloxacin, 1.1% for rifabutin, 0.9% for tetracycline and 0.7% for amoxicillin. A significant association was found between overall fluoroquinolone use in the population and the proportion of *H. pylori* strains exhibiting levofloxacin resistance, similar trends were seen between long-acting macrolide use and clarithromycin resistance.[16]

It is important for clinicians to understand the mechanisms of action of the antibiotics used in *H. pylori* eradication as well as appreciate how *H. pylori* can become resistant to their effects. The main pharmacological targets of antibiotics are the bacterial cell wall, cell membrane and protein or nucleic acid synthesis.[14]

Amoxicillin interferes with peptidoglycan synthesis, through blocking the penicillin-binding proteins (PBP) transporters. This inhibits cell wall synthesis resulting in bacterial dissolution. The rare amoxicillin-resistant *H. pylori* strains harbor mutations in *pbp-1a* (Ser 414 → Arg mutation). Clarithromycin inhibits bacterial protein synthesis through reversibly binding to the bacterial 50S ribosomal subunit. Clarithromycin is unusually acid stable,[17] explains its common use as a bacteriostatic agent in regimens for the elimination of *H. pylori*. The dominant mechanisms underlying the development of clarithromycin resistance are via several point mutations in domain V of the *23S ribosomal RNA* (rRNA) gene, which result in decreased clarithromycin binding to the 50s ribosome subunit.[18] The almost doubling of the prevalence of clarithromycin resistance in Europe over 10 years, from 9.8% to 17.5%,[16,19] has had a major negative impact on the efficacy of clarithromycin-based first-line triple therapy. It is noteworthy that there is cross-resistance among macrolides and that

clarithromycin resistance may originate from the previous widespread consumption of macrolides to treat other infections, especially in the respiratory tract.[20] For this reason, the Maastricht V/Florence Consensus Report and the American College (ACG) Clinical Guideline have recommended abandoning clarithromycin in empirical treatment, or only using it when the prevalence of resistance is known to be lower than 15%.[3,21]

The 5-Nitroimidazoles, among which metronidazole is the most frequently used for *H. pylori* eradication, are prodrugs that when reduced produce oxygen radicals detrimental to bacterial DNA. The nitro-moiety of metronidazole is reduced to a radical anion, and nitroso and hydroxylamine derivatives that cause DNA damage resulting in cell death. Several different mutations and mechanisms contribute to mediate metronidazole resistance. In contrast to clarithromycin resistance, metronidazole resistance, although highly prevalent, can be partly overcome in vivo. Moreover, in some area the clinical response to metronidazole-based regimens has not dropped over the last decade,[22] with no major changes in the regional distribution.

Fluoroquinolones act by inhibiting the A subunit of the enzyme DNA gyrase and interfering with bacterial DNA replication. The main function of this enzyme is to relax the supercoiled DNA allowing its replication. Mutations in the *gyrA* gene are the major cause of *H. pylori* resistance to fluoroquinolones, with cross-resistance among the different fluoroquinolones.

Tetracyclines inhibit protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome. Thus, they prevent introduction of new amino acids to the nascent peptide chain. This action is usually reversible upon withdrawal of the drug. Bacteria usually acquire resistance to tetracyclines from horizontal transfer of a gene that either encodes an efflux pump or a ribosomal protection protein. Efflux pumps actively eject tetracycline from the cell, preventing the buildup of an inhibitory concentration of tetracycline in the cytoplasm. Ribosomal protection proteins interact with the ribosome and dislodge tetracycline from the ribosome, allowing *H. pylori* to survive.

In the last decade, rifabutin-based rescue therapies have offered a promising option after multiple *H. pylori* eradication failures. Rifabutin is an antimycobacterial agent derivative of rifamycin S and targets the DNA-directed RNA polymerase and primarily the ß-subunit encoded by *rpoB.* Resistance to rifabutin is due to mutations at four distinct regions of this gene.[23] Recently, it has been reported that rifabutin-resistant strains of *H. pylori* carried at least one mutation in *rpoB* at codons 525, 530, 538, 540 and a new mutation, L547, has also been detected.[24] Fortunately, selection of *H. pylori* resistant strains to rifabutin remains low under experimental conditions as well as in the clinical setting.

Furazolidone, a nitrofuran agent and monoamine oxidase inhibitor, interferes with the activity of *H. pylori* oxidoreductase, blocking bacterial metabolism of the. This drug has been used to treat diarrhea and enterocolitis caused by bacterial and protozoan infections. Mutations in the genes *porD* and *oorD* of *H. pylori* have been associated with bacterial resistance.[25]

Finally, bismuth salts, though they are not antibiotics, also have antibacterial activity. Bismuth subsalicylate is a colloid of bismuth salicylate hydrolysis. It has been recently shown that bismuth (III) binds to *H. pylori*'s ferric uptake regulator (HpFur) protein specifically at the physiologically important S1 site, which further leads to protein oligomerization and loss of DNA binding capability. The targeting of HpFur significantly reduced transcription levels of its regulated genes, which are crucial for bacterial physiology and metabolism. These data show that perturbation of iron metabolism in *H. pylori,* by bismuth, might serve as one of the mechanisms for the antimicrobial activity of bismuth salts.[26] No resistance has yet been described to bismuth.

Step by step proposal for the treatment of *H. pylori* infection

Opportunities for improvement in clinical practice

Whatever eradication regimen is chosen for a first *H. pylori* treatment, the second regimen should be different. Although this concept may seem obvious, a recent report from Shanghai, China, described

clarithromycin-containing regimens being repeated in 61% and the levofloxacin-containing regimens were repeated in 30.0% of patients who failed a first treatment.[27] Unfortunately, these data are not so different from those observed by some European centers.[28] Thus, there is clearly a need to educate those clinicians that prescribe eradication therapies on the appropriate application of *H. pylori* guidelines.

Moreover, the adherence to recommended regimens could be influenced by the number of treatments, with a reduction of patient compliance in case of repeated regimens.[29]

First-line regimens

Eradication rates with clarithromycin-containing regimens can be predicted if the geographical distribution of clarithromycin resistance is known. The cut off to distinguish regions with low and high clarithromycin resistance has been established as 15%. Although the European[3] and North American (ACG[21] and Toronto[30]) recommendations are similar, the ACG document is more restrictive as it also recommends avoiding clarithromycin triple therapy in patients who have previously received a macrolide treatment for any reason.

- *Countries with low clarithromycin resistance* (<15%)

In these regions the classical triple therapy with PPI, amoxicillin and clarithromycin is recommended both by European and American Guidelines.[3,21] (Fig. 1) As regards the duration of triple therapy, a meta-analysis including 21 randomized controlled trials (RCTs) showed that the rate of eradication was increased by 4% with 10 day compared with 7 day therapy and by 5% comparing 14 with 7 days.[31] Since these results are in agreement with other meta-analyses, today it is recommended to treat for 14 days unless proven otherwise locally. Furthermore, increasing the dose of PPI may increase *H. pylori* eradication rate by 8-12%.[32] and it has been reported that esomeprazole and rabeprazole provide better overall eradication rates than first-generation PPIs.[3]

-Countries with high clarithromycin resistance

In regions with high clarithromycin and metronidazole resistance rates, the bismuth-containing quadruple therapies (with metronidazole and tetracycline) are the first choice, given for 14-days.[3,21,30] (Fig. 2) This regimen is also available using a formulation containing bismuth subcitrate potassium, metronidazole, and tetracycline in a single capsule (three-in-one, Pylera®). This formulation, packaged for 10 days, requires 3 tablets to be taken 4 times a day, and a PPI needs to be taken in addition twice daily. Several reports have demonstrated the efficacy of the three-in-one regimen both in trials and in the real world. In an open-label, randomized, single-arm phase III trial, this formulation of bismuth quadruple therapy given for 10 days achieved *H. pylori* eradication in 80%, *versus* the 55% in the standard 7-day triple therapy group ($p<0.0001$).[33] In one Italian study, *H. pylori* eradication was achieved in 92.7% of naïve patients and this rate was not different from those obtained in previously treated patients ($p=0.383$). Adverse events occurred in 26.7%. They were mild in all cases except in four, who discontinued the study due to diarrhea (three patients) and diffuse urticarial rush (one patient).[34] In a study conducted in two tertiary referral centers in Southern Italy, the population included asymptomatic subjects and patients with *H. pylori*-related symptoms/clinical conditions. All subjects (85/85) treated with the three-in-one regimen obtained *H. pylori* eradication.[35] In contrast, in Lebanese patients with peptic ulcer 14-days sequential therapy was superior to bismuth-containing quadruple therapy (80% *versus* 50%; $p=0.015$).[36] Finally, another Italian study demonstrated similar effectiveness between the three-in-one regimen and the other non-standard therapies. In particular, the eradication rates achieved with three-in-one regimen, concomitant and sequential therapy were 85.2%, 95.2%, and 93.6%, respectively, according to intention to treat (ITT) analysis, and 94.5%, 96.7%, and 95.1% per protocol (PP) analyses, without a statistically significant difference. The incidence of severe side-effects was higher with the bismuth-based therapy than with the two bismuth-free regimens (9.8% *versus* 1.6%; $p=0.046$).[37]

Considering that this drug may not be available in some countries owing to concerns over bismuth toxicity, concomitant, sequential, hybrid or reverse hybrid treatments could be prescribed.[38] Concomitant treatment includes a PPI and three kinds of antibiotics (amoxicillin, clarithromycin and metronidazole) administered together. Sequential therapy comprises 5 days of PPI plus amoxicillin followed by 5 days of PPI, metronidazole and clarithromycin. Hybrid therapy includes PPI and amoxicillin together for 7 days followed by PPI, amoxicillin, metronidazole and clarithromycin for the next 7 days. Reverse hybrid therapy includes PPI plus amoxicillin for 10-14 days with the addition of metronidazole and clarithromycin for the first week.[38] Several trials, systematic reviews and meta-analyses on the efficacy of these new strategies have been published. In a recent systematic review and network meta-analysis, Yeo *et al.* concluded that sequential treatment for 14 days and hybrid therapy for 10 days or more, represented the most effective regimens in areas with high and low clarithromycin resistance, respectively.[39] The strength of network meta-analysis is that rather than comparing trials that evaluated the same treatment, it allows indirect comparisons across trials and among treatments that have not been tested head to head, as long as the trials are linked by a common treatment arm. But there are also several weaknesses inherent in this type of analysis, mainly due to the great variety of study designs, antibiotics types, dosages and administration frequency among the constituent individual studies.[39] Moreover, the lack of information about *H. pylori* sensitivity to antibiotics in several of them is a serious shortcoming that may lead to inappropriate conclusions.[40]

A previous systematic review and meta-analysis compared the results of RCTs in the assessment of the optimal duration of sequential therapy, *versus* 14-day triple therapy as first-line treatment. Including 13 RCTs and more than 2000 patients, sequential therapy given for 14 days was found to be significantly more effective than triple therapy. Important limitations were the open-label design of all included trials and the fact that the better results were obtained in a study conducted in Taiwan, a country with low clarithromycin and metronidazole resistance. [41] In a Cochrane Database of Systematic Reviews, the

ITT eradication rate was reported to better with sequential therapy than with standard triple therapy, though neither regimen achieved optimal efficacy (≥90% eradication rate).[42] According to these results the Maastricht V/Florence Consensus Report did not recommend the use of sequential or hybrid therapies,[3] and the ACG Guideline also stated that 10 day sequential therapy cannot be endorsed as superior to 14 day clarithromycin triple therapy in North America. Regarding hybrid therapy, the ACG Guideline concluded that its complexity may limit its use in routine clinical practice.[21]

Many other alternative approaches have also been proposed, but their results are generally comparable to the established treatments. One example is the recently published modified quadruple therapy (with amoxicillin instead of tetracycline) that was as effective as concomitant therapy in an area with high clarithromycin resistance.[43] In regions with high clarithromycin resistance but low to intermediate metronidazole resistance (<40%), a 14-day regimen of non-bismuth quadruple concomitant therapy is another recommended option.[3]

Second-line regimen

To highlight the difficulties in the management of second-line therapies it should be remembered that in the Maastricht V/Florence Consensus Report, all statements regarding treatment after failure of a first-line regimen have a weak grade of recommendation and a low or very low level of evidence.[3] Hence, the choice of therapy should be adapted to the clinical context.

If there is a reason to do endoscopy, the best and most rational option after the first failure is to use a tailored therapy, that is, to test clarithromycin and other antibiotic susceptibility before prescribing another regimen. Several studies comparing tailored *versus* empiric treatment, have reported a more favorable eradication rate with antimicrobial testing susceptibility.[44] If the strain remains susceptible, another reason other than resistance must be explored, especially compliance. If the strain is resistant, a treatment without clarithromycin must be prescribed.[1,45] Of course, this approach requires the ready

availability of susceptibility testing – either culture based or molecular – which may not be the case in all countries, such as the United States, for example.[21]

After failure of a clarithromycin-based triple therapy, when endoscopy is not being considered, then it is reasonable to assume clarithromycin-resistance and empirically select a second-line treatment that does not include clarithromycin.[3] A levofloxacin-containing triple therapy can be used instead, showing satisfactory results when local fluoroquinolone resistance is <10%.[38] Since the rapid acquisition of levofloxacin resistance may jeopardise its future efficacy, whenever possible it is recommended to test levofloxacin susceptibility before prescribing it.[3] Furthermore, it is advisable to avoid levofloxacin in patients who have previously received fluoroquinolones. Bismuth-based regimens, using traditional bismuth quadruple therapy or the three-in-one formulation represent an excellent choice for second-line therapy too. In this context, Delchier *et al*. conducted a multicenter, open-label, single-arm, multinational study of *H. pylori*-positive subjects who had failed ≥1 previous course of triple clarithromycin-based therapy. Using the three-in-one regimen, *H. pylori* eradication rates ranged from 93.2% to 93.8% in the ITT analysis, and from 94.7% to 95.0% per protocol. The safety profile was good and only one patient discontinued the study for an adverse event.[46]

After failure of a first-line bismuth-based quadruple therapy, a levofloxacin-containing triple or quadruple therapy is recommended. There are no advantages in substituting other fluoroquinolones for levofloxacin.[47]

Finally, after failure of a non-bismuth quadruple therapy, such as concomitant therapy, either a bismuth-based quadruple therapy or a fluoroquinolone-containing regimen are recommended for second-line therapy.[3]

Third-line (and beyond) regimens

After two treatment failures it is highly recommendable to perform antimicrobial susceptibility testing, whenever possible.[3] Levofloxacin-containing regimens are a good choice if the *H. pylori* strain is susceptible, if not, a rifabutin regimen should be considered. Based on data from 2982 patients treated for *H. pylori* infection worldwide, cure rates for second-line, third-line and fourth/fifth-line rifabutin therapies were 79%, 66% and 70%, respectively.[48] The usual dosage of rifabutin is 150 mg twice daily, taken with amoxicillin and a PPI, but the ideal length of treatment remains unclear, 10- to 12-day regimens have generally been recommended. Although rare, myelotoxicity is the most significant complication of rifabutin.[48] Rifabutin resistance is currently low (<5%), but since multidrug resistant mycobacterial strains are rapidly increasing, the use of rifabutin should be restricted to patients who have experienced more than two *H. pylori* treatment failures. As a salvage regimen, furazolidone-based triple therapy has been shown to be effective in some relatively small sized studies. Although this drug has been less studied than rifabutin- and levofloxacin-based treatments, its low cost makes furazolidone-based regimens attractive in developing countries.[38]

After failure of two non-bismuth regimens it is recommended to use a bismuth-based quadruple therapy where possible.[3] Initial studies with the three-in-one regimen reported encouraging data. In a study performed in Germany, of 322 patients treated with this formulation (as first-line, second-line, and salvage treatments in 74%, 17%, and 9% of cases, respectively), 5 discontinued treatment due to side effects (1.8%). By ITT and PP analyses, the overall *H. pylori* eradication rates were 95.0% and 96.7%, respectively.[49] In another study, 116 patients with persistent *H. pylori* infection after at least one eradication therapy attempt were treated. Overall, resistance to clarithromycin was detected in 80% of strains, to metronidazole in 70%, and levofloxacin in 47.5%, with dual or triple resistance in 72.5% of cases. An eradication rate of 81.0% and 87.0% at ITT and PP analyses, respectively, was achieved. The cure rate remained high until it was used as fourth-line regimen, while it dropped to <67. A total of 65.7% patients complained of adverse events.[50] In a study from Spain, in an area of high antibiotic

resistance, a 10-day course with the three-in-one bismuth-based regimen achieved an overall eradication rate of 80.2% by ITT and 84.4% by PP analysis.[51]

After failure of a bismuth-quadruple regimen and a fluoroquinolone-containing therapy, a clarithromycin-based triple or a quadruple therapy are recommended.[3]

Finally, a quintuple therapy (with the addition of bismuth to a concomitant regimen) has been proposed when all else fails. However, the relative costs, side-effects, and the impact of potential antibiotic resistance have not been extensively evaluated with such a regimen.[25]

H. pylori eradication using vonoprazan

One of the most promising advances in *H. pylori* eradication therapy in recent years is the possibility of replacing PPIs with vonoprazan in combination with antibiotics. Although still limited, several recent publications have highlighted the efficacy and safety of vonoprazan in treating *H. pylori* infection. In a phase III clinical study, including patients on first-line therapy, Murakami *et al*. reported an *H. pylori* eradication rate of 92.6% with vonoprazan *versus* 75.9% with lansoprazole.[52] A retrospective review of the medical records of 573 patients treated with triple therapy employing either rabeprazole (10 mg), lansoprazole (30 mg), esomeprazole (20 mg), or vonoprazan (20 mg) showed a superior eradication rate with vonoprazan (83%) compared with lansoprazole (66%) and rabeprazole (67%; $p < 0.01$). No significant difference between esomeprazole and vonoprazan was described.[53] In contrast vonoprazan showed superiority over esomeprazole in a randomized controlled trial of esomeprazole- or rabeprazole-based therapies.[54] Other Japanese studies have reported *H. pylori* eradication rates ranging from 88% to 94% using vonoprazan-based in first-line triple therapy.[12] The adverse effects of vonoprazan-based therapies are comparable to conventional short PPI-based eradication therapies, though long-term studies on the effects of vonoprazan are awaited.[12]

The efficacy of vonoprazan after failure with first-line treatment is largely unknown. Inaba *et al*. investigated the effects of a 1-week treatment with amoxicillin, clarithromycin, and vonoprazan, following the failure of a first-line 1-week treatment with amoxicillin, clarithromycin, and rabeprazole. The results showed that eradication was achieved with the vonoprazan-based therapy for an impressive 70.2% of the cases in which the rabeprazole-based therapy had failed.[55] It is remarkable that the vonoprazan-based treatment showed a relatively high eradication rate even against clarithromycin-resistant *H. pylori.* A plausible explanation is that, since vonoprazan, amoxicillin, and clarithromycin are metabolized by CYP3A4, a combination of these three drugs can delay the clearance of each. In addition, the strength of the acid inhibitory effect of vonoprazan, together with its rapid onset likely increased the ability of the antibiotics, especially amoxicillin, to eradicate *H. pylori*. This raises the possibility that a dual therapy, with vonoprazan and amoxicillin alone, could be sufficient for *H. pylori* eradication.[10] Although this dual regimen required a higher dosing frequency for amoxicillin, 500 mg thrice daily, it achieved *H. pylori* eradication in 95% *versus* 81% of the PPI-based triple therapy.[56] Low rates of *H. pylori* resistance to amoxicillin, together with its ready availability worldwide and its low cost suggest that vonoprazan-amoxicillin dual therapy may be a very useful regimen in the *H. pylori* armamentarium in the future.[12]

Adjuvant treatment

Adding probiotics to *H. pylori* eradication therapies may reduce the adverse effects of antimicrobial regimens and also improve eradication rates. Since these are living bacteria capable of conferring benefits to the host, their administration could have the rationale to compete with *H. pylori* for colonisation and survival.

Systematic reviews and meta-analyses have generally shown beneficial effects of probiotics in improving *H. pylori* eradication, with positive results reported for *Saccharomyces boulardii* (*S. boulardii*), *Lactobacillus* and *Bacillus clausii*. Adding *S. boulardii*, a yeast probiotic, as supplementation to a standard eradication regimen, increased the *H. pylori* eradication rate from 71% to 80% (RR 1.11, 95% CI: 1.06-1.17), based on moderate quality of evidence (assessed by the Grading of Recommendations, Assessment, Development and Evaluation guidelines). Moreover, *S. boulardii* reduced the risk of overall *H. pylori* therapy-related adverse effects, particularly diarrhea and nausea, with high quality of evidence and moderate quality of evidence, respectively.[57] Considering that meta-analyses on the use of *Lactobacillus* have highlighted that studies on this issue are heterogeneous, as they consider different species and strains, additional work needs to be performed to determine optimal strain, dose and duration to be used.[58]

Lactoferrin is an antimicrobial iron-binding protein, found in specific neutrophils granules. The potential role of lactoferrin in improving *H. pylori* treatment outcome has been investigated. Although two meta-analyses showed that lactoferrin increased the efficacy of the standard triple therapy,[59,60] the poor quality of many trials and the limited number of centres involved raise caution regarding a positive endorsement currently.

For now, considering that most trials of adjuvant therapies have an imperfect study design, the main conclusion to be drawn is these novel agents may lead to fewer adverse events, and may thereby only indirectly help improve *H. pylori* eradication rates via improved medication adherence.

Conclusions

What are the main principles that should be applied to address the management of *H. pylori* infection in the year 2018? First, since the decision to test should be made with therapeutic intent, whenever the bacterium is found, it should be treated. Second, before deciding on a specific treatment the patient's

previous antibiotic exposure history should be reviewed. Treatment should also be selected on the basis of local antibiotic resistance and outcome data, with a special focus on clarithromycin-resistance. Third, if the first-line treatment has failed, repeating the same antimicrobial regimen must be avoided. Fourth, as a rescue treatment, when a patient has previously received a clarithromycin-containing regimen, one of the following strategies should be employed: choosing a regimen based on antimicrobial sensitivity testing, or else an empiric bismuth-based quadruple therapy or triple therapy combining a PPI with amoxicillin and levofloxacin. Finally, rifabutin and furazolidone-containing regimens should be considered if the above steps fail.

In the future, vonoprazan may well replace PPIs, especially after one or more unsuccessful eradication attempts. It will also be interesting to explore if and how *H. pylori* eradication could be influenced by or could itself influence the gastric microbiota. The role of the intestinal microbiota is likely to assume great importance as increasing evidence accumulates that gastrointestinal bacteria influence homeostasis, aging and immune, nutritional and neurologic status.[61]

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Figure 1. Optimal therapy for *Helicobacter pylori* eradication in regions with low clarithromycin resistance. Modified from [38].

Figure 2. Optimal therapy for *Helicobacter pylori* eradication in regions with high clarithromycin resistance and variable metronidazole resistance. Modified from [38].